VISUAL OUTCOMES OF AN EXTENDED DEPTH OF FOCUS (EDOF) INTRAOCULAR LENS (IOL)

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Study Product:	AMO - Symfony Toric (ZXT) Intraocular lens
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Investigator Agreement:	I have read the clinical study described herein, recognize its confidentiality and agree to conduct the described trial in compliance with Good Clinical Practices (GCP), the Declaration of Helsinki, this protocol and all applicable regulatory requirements. Additionally, I will comply with all procedures for obtaining informed consent, data recording and reporting, will permit monitoring, auditing, and inspection of my research center, and will retain all records until notified by the sponsor.

Name of the Investigator: _____

Name of the Institution: _____

Address: _____

_____

Principal Investigator: _____

Signature Date

Visual Outcomes of an Extended depth of focus (EDOF) intraocular lens (IOL)

INTRODUCTION

Current visual outcomes expectations of cataract patients are similar to those of refractive surgery patients. Their desire is to be spectacle independent for far, intermediate and near vision activities. Some may have already enjoyed freedom from glasses and would like to continue after the cataracts are removed. Different options are available. These options include: mono-vision and presbyopia correcting intraocular lenses (IOL).

Mono-vision can be achieved by setting the non-dominant eye to -1.75 (range may vary according to patient's preference -1.25 to -2.50 D) and the dominant eye to plano at time of cataract surgery, or postoperatively using contact lenses, or undergoing LASIK.

Presbyopia correcting IOLs include accommodative, multifocals and the recently approved extended depth of focus (EDOF) IOLs.

Accommodative IOLs are design to expand the range of vision by emulating accommodation. The lens is designed to allow the lens optic to move slightly forward with the contraction of the ciliary muscle. The only accommodative IOL approved in the USA is the Crystalens (Bausch and Lomb). In addition to the non-toric model, there is a toric version (Trulign) that is ideal for patients who also have astigmatism. Different studies have shown limited accommodation (0.25 to 0.75 D), which is not optimal, leading surgeons to target slight residual myopia (-0.50 to -0.75) in the non-dominant eye. Tilting and decentration of the IOL due to contraction and fibrosis of the capsular bag have also been reported.

Multifocal IOLs have evolved since they were initially approved by the FDA in 1997 (Array SA40N, Abbott Medical Optics). Multifocal IOLs (MIOL) have been classified based on their design as refractive or diffractive. Refractive MIOL (i.e ReZoom, Abbot Medical Optics) reportedly provided better intermediate vision compared to a diffractive MIOL (i.e ReSTOR, Alcon Laboratories) that provides better near visual acuity. Mixing and matching these 2 lenses was an option to overcome the limitations that each one presented providing patients with improved intermediate and near acuities. The ReSTOR has been modified while the ReZoom IOL was discontinued 1 - 2 years ago. The original ReSTOR had a +4.0 D add delivering good uncorrected distance and uncorrected near visual acuities (UCDVA and UCNVA) but with limited intermediate acuity with a reading distance of 33 cm. Two new ReSTOR models are currently available in the market, a +3.0 D add to enhance the intermediate distance vision with a reading distance of 40 cm, and a +2.5 D add ideal for people who are interested in distance and intermediate vision (50 - 60 cm) activities. Similarly, to mixing and matching, the use of a ReSTOR +3.0 in one eye and the +2.5 in the fellow eye, known as blended vision, is an option to improve patients' vision at the different distances reducing their dependence on glasses.

Another diffractive MIOL is the Tecnis multifocal (Abbott Medical Optics), with a different design than the ReSTOR, is also available in multiple add powers (+4.0 D, +3.25 D and +2.75 D) to meet the needs and preferences of patients. Patients' complaints of glare and halos are common with all MIOLs. The severity of these symptoms vary according to the actual IOL design.

In July 2016, the FDA approved an extended depth of focus (EDOF) IOL (Tecnis Symfony, Abbott Medical Optics) helping to improve the sharpness of vision at near, intermediate and far distances reducing the need of glasses after cataract surgery. It is available in both a non-toric version and a toric version for patients with astigmatism. The difference between this lens and the multifocal counterpart is that the EDOF, similarly to a monofocal IOL, has one focal point (elongated in the EDOF) while the mutifocals have 2 focal points; therefore, having less of a halo and glare problem. Pivotal trial results where Symfony was compared to a monofocal IOL showed similar UCDVA, better intermediate (77% vs. 34% 20/25 UCIVA) and near vision (Symfony patients were able to read two additional, progressively smaller lines compared to the monofoca IOL).[A] One potential disadvantage of the EDOF IOL compared to a MIOL is the visual performance at near.[B] One option to deal with this potential shortcoming is to set the non-dominant eye for a small residual myopic error (-0.50 D)[C] what is referred to as nano-vision or mini mono-vision.

The purpose of this study is to evaluate the visual outcomes of an extended depth of focus (EDOF) IOL when both eyes are targeted for emmetropia and when the non-dominant eye is targeted for nano-vision (-0.50 D) with or without astigmatism after routine cataract surgery.

1. OBJECTIVE:

The main objective of this study is to evaluate the visual outcomes of an extended depth of focus (EDOF) toric IOL when both eyes are targeted for emmetropia and when the non-dominant eye is targeted for nano-vision (-0.50 D) in patients undergoing routine cataract surgery.

2. STUDY DESIGN AND METHODS:

2.1. Test article: Toric Tecnis Symfony IOL (ZXT) (Abbott Medical Optics)

2.2. Study Design: Prospective, multicenter (up to 4 sites in USA), randomized, bilateral eye study.

2.3. Subjects:

1. Inclusion Criteria:

Subjects **MUST** fulfill the following conditions to qualify for enrollment into the trial

1. Subject is undergoing bilateral cataract extraction with intraocular lens implantation.
2. Gender: Males and Females.
3. Age: 40 years and older.
4. Willing and able to provide written informed consent for participation in the study
5. Willing and able to comply with scheduled visits and other study procedures.
6. Scheduled to undergo standard cataract surgery with topical anesthesia in both eyes within 6-15 days between surgeries.

7. Subjects who require an IOL power in the range of +5.0 D to +34.0 D only.
8. Potential postoperative visual acuity of 0.2 logMAR (20/32 Snellen) or better in both eyes.

2. Exclusion Criteria:

Subjects with **ANY** of the following conditions on the eligibility exam may **NOT** be enrolled into the trial.

1. Severe preoperative ocular pathology: amblyopia, rubella cataract, proliferative diabetic retinopathy, shallow anterior chamber, macular edema, retinal detachment, aniridia or iris atrophy, uveitis, history of iritis, iris neovascularization, medically uncontrolled glaucoma, microphthalmos or macrophthalmos, optic nerve atrophy, macular degeneration (with anticipated best postoperative visual acuity less than 20/30), advanced glaucomatous damage, etc.
2. Uncontrolled diabetes.
3. Use of any systemic or topical drug known to interfere with visual performance.
4. Contact lens use during the active treatment portion of the trial.
5. Any concurrent infectious/non-infectious conjunctivitis, keratitis or uveitis.
6. Clinically significant corneal dystrophy
7. History of chronic intraocular inflammation.
8. History of retinal detachment.
9. Pseudoexfoliation syndrome or any other condition that has the potential to weaken the zonules.
10. Previous intraocular surgery.
11. Previous refractive surgery.
12. Previous keratoplasty
13. Severe dry eye
14. Pupil abnormalities
15. Subject who may reasonably be expected to require a secondary surgical intervention at any time during the study (other than YAG capsulotomy, i.e. LASIK)
16. Anesthesia other than topical anesthesia (i.e. retrobulbar, general, etc).
17. Any clinically significant, serious or severe medical or psychiatric condition that may increase the risk associated with study participation or may interfere with the interpretation of study results.
18. Participation in (or current participation) any ophthalmic investigational drug or ophthalmic device trial within the previous 30 days prior to the start date of this trial.

The principal investigator reserves the right to declare a patient ineligible or non-evaluable based on medical evidence that indicates the patient is unsuitable for the trial.

3. Exclusion Criteria during surgery

If any of the following exclusion criteria are applicable to the study eye, the subject should not continue in the study.

1. Other planned ocular surgery procedures, i.e iStent.
2. Significant vitreous loss.
3. Significant anterior chamber hyphema.

4. Uncontrollable intraocular pressure.
5. Zonular or capsular rupture.
6. Bag-sulcus, sulcus-sulcus or unknown placement of the haptics.
7. Suturing of incision required at time of surgery.
8. Intraocular lens tilt or decentration
9. Significant sedation or retrobulbar block during surgery.
10. Other procedure, such as pupil stretch, expanders, iris hooks during surgery.

Note: Any subject in which surgery has been aborted for either eye should immediately be discontinued from the study and an exit form completed for that subject. These subjects will be followed up as per the clinic standard of care, monitored for safety, and their data will be excluded from the study efficacy analysis (obtained from FDA Database Research Results Feb, 05, 2009). All adverse events will be appropriately documented and reported.

Additionally, participants who are considered to be a vulnerable subject population are not to be enrolled into the study without prior written authorization from both the Sponsor and the IRB to ensure that a description of additional safeguards are in place during the consenting and enrollment processes. Vulnerable populations include, but are not limited to, the following:

1. Prisoners
2. Nursing home residents /institutionalized individuals
3. Mentally disabled /cognitively impaired individuals
4. Sponsor employees and their family members
5. Site employees and their family members that are directly and indirectly involved with the study
6. Students of the university or the principal investigator participating in the study
7. Economically and/or educationally disadvantaged individuals
8. Comatose individuals / traumatized individuals
9. Adults who do not read and/or write
10. Hearing impaired individuals
11. Terminally ill individuals / individuals with life-threatening conditions

3. Study Procedures

3.1. Informed Consent / Subject enrollment

Potential subjects will be identified from the patients presenting at the clinic. Additionally, an ad will be placed in the local newspaper and in the practice website. Once identified as a study candidate, the patient will be asked if he/she would like to participate. The sub-investigator, study coordinator or an appropriately trained staff member will answer any and all questions and will obtain informed consent. A copy of the signed informed consent document will be given to the subject. The principal investigator will be available if the subject wants to discuss further details with him. Any testing that is part of the investigative site's standard preoperative cataract evaluation may be performed prior to the informed consent being signed, provided these tests are conducted within 90 days of surgery. The patient will

understand that participation in the study, or declining to participate, will not affect his/her quality of care.

No subject will be enrolled into the study that does not meet the inclusion/exclusion criteria and does not sign the current approved informed consent document. Informed consent will be obtained prior to collecting any data for the study. The original signed documents will be maintained by the investigator as a permanent part of the subject's research records and a scanned copy will be uploaded to the subject's electronic medical record.

3.2. Surgery Procedures:

Patients will be randomized to one of two groups:

- Group A, plano OU. The target refraction for both eyes will be emmetropia (± 0.25 D).
- Group B, nano-vision. The target refraction for the dominant eye will be plano and for the non-dominant eye -0.50 ±0.16 D.

3.3. Study Visit Schedule and Assessments (Table 1).

1. **Visit Schedule:** Subjects will be examined at the following intervals:

1. Visit 1: Screening and enrollment: Preoperative evaluation completed not more than eight weeks before surgery
2. Visit 2: Day of Surgery
3. Visit 3: Day 1: (12 to 48 hours) after surgery
3. Visit 4: Month 1: 30 ±5 days postoperative after second eye surgery
4. Visit 5: Month 3: 90 ±15 days postoperative after second eye surgery

3.4. Measurements and evaluations

1. Visit 1: Informed consent process will be conducted at this visit. Assessments include uncorrected and best-corrected ETDRS visual acuity at 4 m (UCVA / BCVA), manifest refraction, intraocular pressure (IOP) using Goldman tonometer, corneal topography, undilated photopic and mesopic pupil size, slit lamp examination including dilated fundus exam, cataract density and type, and HD analyzer. Any testing that is part of the site's standard of care preoperative cataract surgery evaluation may be performed prior to the informed consent being signed provided these tests are conducted within 90 days of the surgery and notation of the date performed is entered onto the CRF. The surgeon's standard pre cataract surgery treatment will be used in all his patients

   Each subject will be randomized to Group A or B. Randomization will ensure that an equal number of subjects are enrolled in each group.

2. Visit 2: The surgeon may use his preferred cataract extraction technique (manual or laser). The lens will be implanted in the bag. The following information will be captured the day of surgery: phaco technique (manual or laser), lens implanted and power, target refraction for

IOL power implanted, additional surgical procedures, intraoperative complications, and any device deficiencies. The surgeon's standard post cataract surgery treatment will be used in all his patients. IOL power changes based on intraoperative aberrometry (i.e. ORA) are not allowed but it can be used to align the lens.

3. Visit 3: monocular UCVA, slit lamp examination, IOP, and lens orientation (measured using slit lamp photography).

4. Visit 4: Slit lamp examination, manifest refraction, UCVA, BCVA, UCIVA (at 66 cm), DCIVA (at 66 cm), UCNVA (at 40 cm), DCNVA (at 40), and UCNVA at best distance, undilated photopic and mesopic pupil size, IOP, IOL orientation (measured using slit lamp photography), dilated fundus exam (as deem necessary by the investigator), patient satisfaction, visual symptoms and spectacle independence questionnaires, HD Analyzer, and any device deficiencies.

5. Visit 5: Slit lamp examination, manifest refraction, UCVA, BCVA, UCIVA (at 66 cm), DCIVA (at 66 cm), UCNVA (at 40 cm) and DCNVA (at 40), and UCNVA at best distance, undilated photopic and mesopic pupil size, IOP, IOL orientation (measured using slit lamp photography), reading speed, defocus curve, dilated fundus exam (as deem necessary by the investigator), patient satisfaction, visual symptoms and spectacle independence questionnaires, HD Analyzer, keratometry measurement with the device used to calculate the toric power, and any device deficiencies.

All adverse events and complaints will be monitored and recorded at all study visits.

Table 1. Visits and Study Assessments

	Visit 1 Screening	Visit 2 DOS	Visit 3 POD #1	Visit 4 1-Month	Visit 5 3-Month
Informed Consent	X				
Inclusion/Exclusion	X				
Demographics/PMH/Ocular history	X				
UCVA ETDRS (4m)	X		X	X*	X**
Manifest refraction – Max Plus	X			X	X
BCVA ETDRS (4m)	X			X*	X**
UCIVA ETDRS (66 cm)				X*	X**
DCIVA ETDRS (66 cm)				X*	X**
UCNVA ETDRS (40 cm)				X*	X**
DCNVA ETDRS (40 cm)				X*	X**
UCNVA at best distance				X*	X**
Reading speed					X**
Defocus curve					X**

Intraocular Pressure (Goldman)	X		X	X	X
SLE	X		X	X	X
Dilated fundus exam	X			X†	X†
Cataract density / type	X				
Corneal topography	X				
Undilated photopic and mesopic pupil size	X			X	X
Intraop data		X			
Toric IOL position		X	X	X	X
Questionnaires				X	X
HD Analyzer	X			X	X
keratometry measurement with the device used to calculate the toric power					X
AE/Device deficiencies		X	X	X	X

X To be performed as scheduled
* Monocular and binocular testing
** Binocular testing only
† To be performed as deem necessary by the investigator.

4. Study endpoint criteria

4.1. Patient Completion of Study: If a study patient has completed the final visit (Visit 5) of the study, he/she is considered to have completed the study.

4.2. Patient Discontinuation: Each study patient may voluntarily discontinue the study at any time they choose. Study patients who cannot complete the study for administrative reasons (e.g., non-compliance, failure to meet visit schedule, etc.) will be discontinued from the study. Study patients discontinued during the enrollment phase (prior to surgery) of the study will be replaced.

4.3. Patient Termination: A study patient will be terminated if the study patient develops any severe adverse event that may be related to the study. A study patient will receive appropriate treatment at the discretion of the investigator. Notification of termination will be clearly documented. These study patients are considered to have completed the study and will not be replaced.

4.4. Study Termination: The investigator with appropriate notification may terminate the study. If, after clinical observations, the investigator feels that it may be unwise to continue the study, he may stop the study.

4.5. Study Completion: The study will be complete when all enrolled patients have completed Visit 5 or have been terminated from the study.

5. STATISTICAL CONSIDERATIONS

5.1. Sample size

The sample size estimates depend in large part on the standard deviation (SD) for logmar UCVA. Assuming a SD of 0.16 (mean from previous Symfony studies)), for the two-sided t-test (alpha =0.05) for the near visual acuity endpoint, we will need 55 subjects in each group (emmetropia / nano-vision) to detect differences of 0.1 logMAR with 90% power. Total sample size = 110. Allowing 10 % for the potential confounding factor of having 4 sites, 120 subjects will be enrolled (60 in each group). Table 2 summarizes the sample size estimate.

Table 2. Sample size estimate.

	Toric Group	
	Emmetropia	**Nano-Vision**
Sample size	55	55
5% multiple sites	5	5
Total sample size	60	60

5.2. Statistical Analysis

All data will be collected by the site and entered into a database. Subjects will be assigned an ID number. Data analysis will be performed without patient identification. Statistical analysis will be performed using standard descriptive statistics and other tests as deemed appropriate based on the characteristics of the data to be analyzed. All statistical tests will be two-sided and interpreted at a 5% significance level. Comparisons between the groups will be made. Data analysis will be conducted by a third party consultant.

5.3. Study Endpoints:

Comparisons between the groups:

1. **Primary Endpoints:**
   - Binocular distance-corrected near (40 cm) visual acuity.

- Reduction of astigmatism.

2. **Secondary Endpoints:**
   - Uncorrected and distance-corrected near (40 cm) visual acuity at 1 month and 3 months
   - Uncorrected and distance-corrected intermediate (66 cm) visual acuity at 1 month and 3 months
   - Uncorrected and best-corrected distance (4 m) visual acuity at 1 month and 3 months
   - To evaluate patient's overall satisfaction of their vision
   - To evaluate patient's spectacle independence
   - To evaluate visual symptoms using a questionnaire.
   - Residual mean spherical equivalent refraction at 1 and 3 months
   - Residual refractive sphere at 1 month and 3 months
   - Residual refractive cylinder at 1 month and 3 months
   - Percentage of eyes with postoperative MRSE accuracy to target ≤ 0.5D at 1 and 3 months
   - Determine stability of toric iol from time of surgery to 3 months postoperative
   - To evaluate the surgeons experience and overall satisfaction

5.4. Safety Analyses

The type, severity, duration and frequency of reported ocular adverse events will be tabulated for each group. Adverse events will also be summarized for events that were considered treatment-related. Comparison of treatment groups with respect to the proportion of study patients reporting adverse events will be made using Fisher's Exact Test.

6. DATA HANDLING AND RECORD KEEPING

6.1. Confidentiality

To ensure confidentiality in this study, records of the participants will be examined only by the principal investigator and research staff involved in the study. Study records will be kept on file at each site. Any statistical analysis and publication will not include any subject identifiers. Medical records will be made available only for review by the investigators, study Monitor or Auditor, Sponsor Company or Research Institution, the IRB, and other State or Federal Regulatory Agencies, if necessary. All information in these records will be kept confidential.

6.2. Records Retention

The PI is accountable for the integrity, retention and security of all study related data. The investigator must maintain accurate, complete and current records relating to the clinical study. The investigator must maintain the required records during the investigation and for a period of 1 year after the date on which the investigation is terminated or completed.

7. STUDY MONITORING, AUDITING, AND INSPECTING

The nature and location of all source documents will be identified to ensure that original data required to complete the case report forms (CRFs) exist and are accessible for verification by the monitor. If electronic source records are maintained, these records must be 21 CFR Part 11 compliant and will be printed and certified for verification by the monitor as needed.

Required examination must be recorded on the CRFs. Provided CRFs can be used as source document. All data reported must have corresponding entries in the source documents. The principal investigator or sub-investigator must review the reported data and certify that the CRFs are accurate and complete. No subject identifiers should be recorded on the CRFs beyond subject number, subject initials and study specific identifiers.

Data from CRFs will be entered into a database provided to each site, site will email the password protected file to the study manager with the CRFs for remote monitoring. Additionally, monitoring site visits will be made by the study manager throughout the study.

Upon completion of the CRFs, the data will be reviewed by study manager and statistician for accuracy and completeness. If corrections and/or any additions to the data are deemed necessary, queries will be generated and forwarded to the investigative site. Designated research staff expected to respond to data queries in a timely manner and ensure that the corrections and changes made to the data in the database are reflected in the subjects' source documentation. Any changes will need to be initialed and dated by the authorized personnel making such changes.

Data will not be sold to third parties nor will it be used for future research.

Electronic data will be stored and accessed on a portable device. The laptop is password protected and only the study manager has access to it. Additionally, database will be password protected.

8. INVESTIGATIONAL PRODUCT

8.1. Description

The Symfony Toric IOL (ZXTx) is an extended depth of focus (EDOF) IOL design to improve the sharpness of vision at near, intermediate and far distances reducing the need of glasses after cataract surgery in patients with astigmatism. The EDOF IOL, similarly to a monofocal IOL, has one

focal point, it is elongated in the EDOF, having less of a halo and glare problem compared to multifocal IOLs.

8.2. Treatment/Dosing Regimen

The Symfony Toric IOL (ZXTx) is intended for primary implantation for the visual correction of aphakia secondary to removal of a cataractous lens in adult patients. The IOL will be implanted at time of uncomplicated routine cataract surgery. Intraocular lenses are implantable medical devices and are intended for long term use over the lifetime of the patient.

8.3. Method for Assigning Subjects to Treatment/Dosing Groups

The statistician will provide randomization envelopes. The envelopes will be sequentially numbered and they will be provided to each site.

8.4. Subject Compliance Monitoring

Since the IOL is implanted at time of cataract surgery, subject compliance will not be an issue in this particular study.

8.5. Packaging, Receiving, Storage, Dispensing and Return

An account will be set up with the manufacturer of the lens (Abbott Medical Optics - AMO) that will provide the lens at no cost to the participants. IOLs will be ordered once the subjects qualification for the study has been confirmed. IOLs will be shipped to the site or ambulatory surgery center and will be stored and dispensed following the routine standard of care for cataract surgery. Unused IOLs will be returned to AMO following their instructions.

9. ETHICAL CONSIDERATIONS

This clinical trial will be conducted in accordance with the principles of the Declaration of Helsinki, and Good clinical practice. The Investigator and all clinical trial staff will conduct the clinical trial in compliance with this protocol. The Investigator will ensure that all personnel involved in the conduct of the clinical trial are qualified to perform their assigned duties through relevant education, training, and experience. Deviations from the clinical protocol must be documented in each subject's study records including the dates and reasons for each deviation. The PI must ensure that all aspects of the trial are in compliance with the applicable regulatory laws and conditions of approval imposed by the IRB.

10. IN CASE OF AN INJURY RELATED TO THIS RESEARCH STUDY

Every effort to prevent study-related injury will be taken by the study doctor and staff. In the event a patient is injured as a direct result of the study while following the study instructions and requirements, the patient will be instructed to immediately contact the principal investigator and/or study staff. Treatment will be provided as needed for those injuries caused directly by this research

study. In the event of injury or illness caused by or occurring during the participation in this study, all charges for medical care provided will be billed to the patient's insurance company. The medical care costs for injuries or illnesses that are not caused directly by the research study will not be covered.

11. CONFIDENTIALITY/PUBLICATION OF THE STUDY

The existence of this Study is confidential and should not be discussed with persons outside of the Study. Results will be submitted for publication and presentation at national and/or international meetings. A manuscript will be submitted to peer-review journals for publication but there is no guarantee of acceptance.

12. REFERENCES

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B. http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM391594.pdf. Accessed 09/20/2016.
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